Annex XI

USA Comments

CHAPTER 6.9.

General Comment on syntax: In this chapter (English version), "(s)" is deleted in many places throughout the document. In some cases, it looks like only the parentheses are deleted, but it is hard to determine that. In many cases, it is not appropriate to delete the "s" without adding an "an" or "a" prior to the word from which it was deleted. An editor should review these proposed deletions throughout the document.

RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE

Article 6.9.1.

Purpose

This document provides guidance for the responsible and prudent use of *antimicrobial agents* in veterinary medicine, with the aim of protecting both animal and human health as well as the environment. It defines the respective responsibilities of the *Competent Authority* and stakeholders such as the veterinary pharmaceutical industry, *veterinarians*, animal feed manufacturers, distributors and food animal producers who are involved in the authorisation, production, control, importation, exportation, distribution and use of *veterinary medicinal products* (VMP) containing *antimicrobial agent~~(s)~~*.

Responsible and prudent use is determined taking into account the specifications detailed in the marketing authorisation and their implementation when *antimicrobial agents* are administered to *animals* and is part of good veterinary and good agricultural practice.

Activities associated with the responsible and prudent use of *antimicrobial agents* should involve all relevant stakeholders.

Coordination of these activities at the national or regional level is recommended and may support the implementation of targeted actions by the stakeholders involved and enable clear and transparent communications.

Article 6.9.2.

Objectives of responsible and prudent use

Responsible and prudent use includes implementing practical measures and recommendations intended to improve animal health and *animal welfare* while preventing or reducing the selection, emergence and spread of antimicrobial-resistant bacteria in *animals* and humans. Such measures include:

1) ensuring the rational use of *antimicrobial agents* in *animals* with the purpose of optimising both their efficacy and safety;

2) complying with the ethical obligation and economic need to keep *animals* in good health;

3) preventing or reducing, as far as possible, the transfer of resistant micro-organisms or resistance determinants within animal populations, the environment and between *animals* and humans;

4) contributing to the maintenance of the efficacy and usefulness of *antimicrobial agents* used in animal and human medicine;

5) protecting consumer health by ensuring the safety of food of animal origin with respect to residues of *antimicrobial agents*.

Comment: Although not an item for current comment, this Article is focused on “resistance”. Does the term “residues here meant to include resistance determinants? If not, then this point should be modified to include the phrase “biologically active” residues.

Article 6.9.3.

Responsibilities of the Competent Authority

1. Marketing authorisation

All Member Countries should combat the unauthorised manufacture, compounding, importation, advertisement, trade, distribution, storage and use of unlicensed, adulterated and counterfeit products, including bulk active ingredients, through appropriate regulatory controls and other measures.

Annex XI (contd)

The *Competent Authority* is responsible for granting marketing authorisation which should be done in accordance with the provisions of the *Terrestrial Code*. It has a significant role in specifying the terms of this authorisation and in providing the appropriate information to *veterinarians* and all other relevant stakeholders.

The *Competent Authority* should establish and implement efficient statutory registration procedures that evaluate the quality, safety and efficacy of VMP containing *antimicrobial agent~~(s)~~*. According to Article 3.1.2., the *Competent Authority* should be free from any commercial, financial, hierarchical, political or other pressures which might affect its judgement or decisions.

Member Countries lacking the necessary resources to implement an efficient registration procedure for VMP containing *antimicrobial agent~~(s)~~*, and which are importing them, should undertake the following measures:

a) evaluate the efficacy of administrative controls on the import of these VMP;

b) evaluate the validity of the registration procedures of the exporting and manufacturing country as appropriate;

c) develop the necessary technical co-operation with experienced relevant authorities to check the quality of imported VMP as well as the validity of the recommended conditions of use.

The *Competent Authorities* of *importing countries* should request the pharmaceutical industry to provide quality certificates prepared by the *Competent Authority* of the exporting and manufacturing country as appropriate.

Marketing authorisation is granted on the basis of the data submitted by the pharmaceutical industry or applicant and only if the criteria of safety, quality and efficacy are met.

Member Countries are encouraged to apply the existing guidelines established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

An evaluation of the potential risks and benefits to both *animals* and humans resulting from the use of *antimicrobial agents*, with particular focus on use in food producing animals, should be carried out. The evaluation should focus on each individual *antimicrobial agent* and the findings should not be generalised to the antimicrobial class to which the particular active ingredient belongs. Guidance on usage should be provided for all target species, route of administration, dosage regimens, withdrawal period and different durations of treatment that are proposed.

The *Competent Authority* should expedite the process for new *antimicrobial agent~~(s)~~* in order to address a specific need for the treatment of *animal disease*.

2. Quality control of antimicrobial agent~~(s)~~ and VMP containing antimicrobial agent~~(s)~~

Quality controls should be performed:

a) in compliance with the provisions of *good manufacturing practices*;

b) to ensure that analysis specifications of *antimicrobial agent~~(s)~~* used as active ingredients comply with the provisions of registration documentations (such as monographs) approved by the relevant *Competent Authority*;

c) to ensure that the quality of *antimicrobial agent~~(s)~~* in the marketed dosage form~~(s) are~~ is maintained until the expiry date, established under the recommended storage conditions;

d) to ensure the stability of *antimicrobial agent~~(s)~~* when mixed with feed or drinking water **when indicated**;

Rationale: suggest that the term "when indicated" be added since stability in feed may not be relevant for some instances.

e) to ensure that all *antimicrobial agent~~(s)~~* and the VMP containing them are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

3. Assessment of therapeutic efficacy

a) Preclinical trials

i) Preclinical trials should:

- establish the spectrum of activity of *antimicrobial agent~~(s)~~* against relevant pathogens and non-pathogens (commensals);
- assess the capacity of the *antimicrobial agent~~(s)~~* to select for resistance *in vitro* and *in vivo*, taking into consideration intrinsically resistant and pre-existing resistant strains;
- establish an appropriate dosage regimen (dose, dosing interval and duration of the treatment) and route of administration necessary to ensure the therapeutic efficacy of the *antimicrobial agent~~(s)~~* and limit the selection of antimicrobial resistance. Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal.

ii) The activity of *antimicrobial agent~~(s)~~* towards the targeted microorganism should be established by pharmacodynamics. The following criteria should be taken into account:

- spectrum of activity and mode of action;
- minimum inhibitory and bactericidal concentrations against recent isolates;
- time- or concentration-dependent activity or co-dependency;
- activity at the site of *infection*.

iii) The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

- bio-availability according to the route of administration;
- distribution of the *antimicrobial agent~~(s)~~* in the treated *animal* and concentration at the site of *infection*;
- metabolism;
- excretion routes.

Use of combinations of *antimicrobial agents* should be scientifically supported.

b) Clinical trials

Clinical trials in the target animal species should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

i) diversity of the clinical cases encountered when performing multi-centre trials;

ii) compliance of protocols with good clinical practice;

iii) eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;

iv) parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

4. Assessment of the potential of antimicrobial agent~~(s)~~ to select for resistance

Other studies may be requested in support of the assessment of the potential of *antimicrobial agents* to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered:

a) the concentration of either active *antimicrobial agent~~(s)~~* or metabolite~~(s)~~ in the gut of the *animal* (where the majority of potential foodborne pathogens reside) at the defined dosage level;

b) pathway for the human exposure to antimicrobial resistant microorganisms;

c) the degree of cross-resistance;

d) the intrinsic and pre-existing, baseline level of resistance in the pathogens of human health concern in both *animals* and humans.

5. Establishment of acceptable daily intake (ADI), maximum residue limit (MRL) and withdrawal periods in food producing animals

a) When setting the ADI and MRL for an *antimicrobial agent*, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.

b) The establishment of an ADI for each *antimicrobial agent*, and an MRL for each animal-derived food, should be undertaken before a VMP containing it is granted marketing authorisation.

c) For all VMP containing *antimicrobial agent~~(s)~~*, withdrawal periods should be established for each animal species in order to ensure compliance with the MRLs, taking into account:

i) the MRLs established for the *antimicrobial agent* in the target animal edible tissues;

ii) the composition of the product and the pharmaceutical form;

iii) the dosage regimen;

iv) the route of administration.

d) The applicant should describe methods for regulatory testing of residues in food based on the established marker residues.

6. Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted.

7. Establishment of a summary of product characteristics for each VMP containing antimicrobial agent~~(s)~~

The summary of product characteristics contains the information necessary for the appropriate use of VMP containing *antimicrobial agent~~(s)~~* and constitutes the official reference for their labelling and package insert. This summary should contain the following items:

a) active ingredient and class;

b) pharmacological properties;

c) any potential adverse effects;

d) target animal species and, as appropriate, age or production category;

e) therapeutic indications;

f) target micro-organisms;

g) dosage regimen and route of administration;

h) withdrawal periods;

i) incompatibilities and interactions;

j) storage conditions and shelf-life;

k) operator safety;

l) particular precautions before use;

m) particular precautions for the proper disposal of un-used or expired products;

n) information on conditions of use relevant to the potential for selection of resistance;

o) contraindication.

8. Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, and any other relevant scientific data, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this, the following should be considered:

a) General epidemiological surveillance

The surveillance of animal microorganisms resistant to *antimicrobial agent~~(s)~~* is essential. The relevant authorities should implement a programme according to Chapter 1.4.

b) Specific surveillance

Specific surveillance to assess the impact of the use of a specific *antimicrobial agent* may be implemented after the granting of marketing authorisation. The surveillance programme should evaluate not only resistance in target animal pathogens, but also in foodborne pathogens, and commensals if relevant and possible. This will also contribute to general epidemiological surveillance of antimicrobial resistance.

9. Supply and administration of the VMP containing antimicrobial agent~~(s)~~

The relevant authorities should **strive to** ensure ~~that all~~ the VMP containing *antimicrobial agent~~(s)~~* used in *animals* are:

Rationale: The United States believe the current language to be prescriptive. Suggested indicated changes are more goal-oriented. Also, the word "all" is too broad in scope. For example, should 'ionophores' included?

a) prescribed by a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agent~~(s)~~* in accordance with the national legislation and under the supervision of a *veterinarian*;

b) supplied only through licensed or authorised distribution systems;

c) administered to *animals* by a *veterinarian* or under the supervision of a *veterinarian* or by other authorised persons.

The relevant authorities should develop effective procedures for the safe collection and disposal or destruction of unused or expired VMPs containing *antimicrobial agent~~(s)~~*. Their labels should have appropriate instructions for disposal and destruction.

10. Control of advertising

All advertising of *antimicrobial agents* should be compatible with the principles of responsible and prudent use and should be controlled by codes of advertising standards. The relevant authorities must ensure that the advertising of these products:

a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;

Annex XI (contd)

b) is restricted to a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agent~~(s)~~* in accordance with the national legislation and under the supervision of a *veterinarian*.

11. Training on the usage of antimicrobial agents

The training on the usage of *antimicrobial agents* should include all the relevant organisations, such as the *Competent Authority*, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food animal owners and manufacturers of medicated animal feed. This training should focus on preserving the effectiveness of *antimicrobial agents* and include:

a) information on *disease* prevention, management and mitigation strategies;

b) the ability of *antimicrobial agent~~(s)~~* to select for resistant microorganisms in *animals* and the relative importance of that resistance to public and animal health;

c) the need to observe responsible use recommendations for the use of *antimicrobial agent~~(s)~~* in animal husbandry in agreement with the provisions of the marketing authorisations;

d) appropriate storage conditions, proper disposal of unused or expired VMP;

e) record keeping.

12. Research

The relevant authorities should encourage public- and industry-funded research, for example on methods to identify and mitigate the public health risks associated with specific *antimicrobial agent* uses, or on the ecology of antimicrobial resistance.

Article 6.9.4.

Responsibilities of the veterinary pharmaceutical industry with regards to VMP containing antimicrobial agent~~(s)~~

1. Marketing authorisation

The veterinary pharmaceutical industry has responsibilities to:

a) supply all the information requested by the national *Competent Authority*;

b) guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;

c) implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance data.

2. Marketing and export

For the marketing and export of VMP containing *antimicrobial agent~~(s)~~*:

a) only licensed and officially approved VMP containing *antimicrobial agent~~(s)~~* should be sold and supplied, and then only through licensed/authorised distribution systems;

b) the pharmaceutical industry should provide quality certificates prepared by the *Competent Authority* of the exporting and manufacturing countries to the *importing country*;

c) the national regulatory authority should be provided with the information necessary to evaluate the amount of *antimicrobial agents* marketed.

3. Advertising

The veterinary pharmaceutical industry should respect principles of responsible and prudent use and should comply with established codes of advertising standards, including to:

a) distribute information in compliance with the provisions of the granted authorisation;

b) discourage the advertising of VMP containing *antimicrobial agent~~(s)~~* directly to the food animal producer.

4. Training

The veterinary pharmaceutical industry should participate in training programmes as defined in point 14 of Article 6.9.3.

5. Research

The veterinary pharmaceutical industry should contribute to research as defined in point 15 of Article 6.9.3.

Article 6.9.5.

Responsibilities of wholesale and retail distributors

1. Distributors of VMP containing *antimicrobial agent~~(s)~~* should only do so on the prescription of a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agent~~(s)~~* in accordance with the national legislation and under the supervision of a *veterinarian*. All products should be appropriately labelled.

2. The recommendations on the responsible and prudent use of VMP containing *antimicrobial agent~~(s)~~* should be reinforced by retail distributors who should keep detailed records of:

a) date of supply;

b) name of prescriber;

c) name of user;

d) name of product;

e) batch number;

f) expiration date;

g) quantity supplied;

h) copy of prescription.

3. Distributors should also be involved in training programmes on the responsible and prudent use of VMP containing *antimicrobial agent~~(s)~~*, as defined in point 14 of Article 6.9.3.

Article 6.9.6.

Responsibilities of veterinarians

The *veterinarian*'s responsibility is to promote public health, animal health and *welfare*, including identification, prevention and treatment of animal *diseases*. The promotion of sound animal husbandry methods, hygiene procedures, biosecurity and *vaccination* strategies can help to minimise the need for antimicrobial use in food producing *animals*.

Annex XI (contd)

Veterinarians should only prescribe *antimicrobial agent(s)* for *animals* under their care.

1. Use of antimicrobial agent(s)

   The responsibilities of *veterinarians* are to carry out a proper clinical examination of the *animal(s)* and then:

   a) administer or prescribe *antimicrobial agent(s)* only when necessary and taking into consideration the OIE list of *antimicrobial agents* of veterinary importance;

   b) make an appropriate choice of *antimicrobial agent(s)* based on clinical experience and diagnostic laboratory information (pathogen isolation, identification and antibiogram) where possible;

   c) provide a detailed treatment protocol, including precautions and withdrawal times, especially when prescribing extra-label or off-label use.

2. Choosing antimicrobial agent(s)

   a) The expected efficacy of the treatment is based on:

      i) the clinical experience of the *veterinarians,* their diagnostic insight and therapeutic judgement;

      ii) diagnostic laboratory information (pathogen isolation, identification and antibiogram);

      iii) pharmacodynamics including the activity towards the pathogens involved;

      iv~~ii~~) the appropriate dosage regimen and route of administration;

      ~~i~~v) pharmacokinetics and tissue distribution to ensure that the selected therapeutic agent is effective at the site of *infection*;

      vi) the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens involved.

      Should a first-line antimicrobial treatment fail or should the *disease* recur, a second line treatment should ideally be based on the results of diagnostic tests. In the absence of such results, an appropriate *antimicrobial agent* belonging to a different class or sub-class should be used.

      In emergencies, a *veterinarian* may treat *animals* without recourse to an accurate diagnosis and antimicrobial susceptibility testing, to prevent the development of clinical *disease* and for reasons of *animal welfare*.

   b) Use of combinations of *antimicrobial agents* should be scientifically supported. Combinations of *antimicrobial agents* may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

3. Appropriate use of the VMP~~s~~ containing antimicrobial agent(s) chosen

   A prescription for VMP containing *antimicrobial agent(s)* should indicate precisely the dosage regimen, the withdrawal period where applicable and the amount of VMP containing *antimicrobial agent(s)* to be provided, depending on the dosage and the number of *animals* to be treated.

   The extra-label or off-label use of VMP containing *antimicrobial agent(s)* may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used, as applicable. It is the *veterinarian*'s responsibility to define the conditions of responsible use in such a case including the dosage regimen, the route of administration and the withdrawal period.

   The use of compounded VMP containing *antimicrobial agent(s)* and extra-label or off-label use of registered VMP containing *antimicrobial agent(s)* should be limited to circumstances where an appropriate registered product is not available.

4. Recording of data

Records on VMP containing *antimicrobial agent~~(s)~~* should be kept in conformity with the national legislation. Information records should include the following:

a) quantities of VMP used per animal species;

b) a list of all VMP supplied to each food producing animal holding;

c) treatment schedules including animal identification and withdrawal period;

d) antimicrobial susceptibility data;

e) comments concerning the response of *animals* to treatment;

f) the investigation of adverse reactions to antimicrobial treatment, including lack of response due to possible antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

Veterinarians should also periodically review farm records on the use of VMP containing *antimicrobial agent~~(s)~~* to ensure compliance with their directions or prescriptions and use these records to evaluate the efficacy of treatments.

5. Labelling

All VMP supplied by a *veterinarian* should be labelled according to the national legislation.

6. Training and continued professional development

Veterinary professional organisations should participate in the training programmes as defined in point 14 of Article 6.9.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice recommendations on the responsible and prudent use of VMP containing *antimicrobial agent~~(s)~~*.

Article 6.9.7.

Responsibilities of food-animal producers

1) Food animal producers, with the assistance and guidance of a *veterinarian,* are responsible for implementing animal health and *welfare* programmes on their farms in order to promote animal health and food safety.

2) Food animal producers should:

a) draw up a health plan with the attending *veterinarian* that outlines preventive measures (e.g. feedlot health plans, mastitis control plans, endo- and ectoparasite control, *vaccination* programmes and biosecurity measures);

b) use VMP containing *antimicrobial agent~~(s)~~* only on the prescription of a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agent~~(s)~~* in accordance with the national legislation and under the supervision of a *veterinarian*;

c) use VMP containing *antimicrobial agent~~(s)~~* in accordance with product label instructions, including storage conditions, or the instructions of the attending *veterinarian*;

d) isolate sick *animals*, when appropriate, to avoid the transfer of pathogens; dispose of dead or dying *animals* promptly under conditions approved by the relevant authorities;

e) address on-farm biosecurity measures and take basic hygiene precautions as appropriate;

f) comply with and record the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;

Annex XI (contd)

g) use VMP containing *antimicrobial agent~~(s)~~* within the expiry date and dispose of unused and expired surplus VMP containing *antimicrobial agent~~(s)~~* under conditions safe for the environment;

h) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the *veterinarian* responsible for treating the *animals*;

i) keep adequate records of all VMP containing *antimicrobial agent~~(s)~~* used, including the following:

i) name of the product and active substance, batch number and expiry date;

ii) name of prescriber and the supplier;

iii) date of administration;

iv) identification of the *animal* or group of *animals* to which the *antimicrobial agent* was administered;

v) clinical conditions treated;

vi) dosage;

vii) withdrawal periods including the end-date of the withdrawal periods;

viii) result of laboratory tests;

ix) effectiveness of therapy;

j) inform the responsible *veterinarian* of recurrent *disease* problems.

3) Training

Food animal producers should participate in the training programmes as defined in point 14 of Article 6.9.3. It is recommended that food animal producer organisations work in cooperation with the veterinary professional organisations to implement existing guidelines for the responsible and prudent use of VMP~~s~~ containing *antimicrobial agent~~(s)~~*.

Article 6.9.8.

Responsibilities of animal feed manufacturers

1) The supply of medicated feed containing *antimicrobial agents* to farmers keeping food producing animals by animal feed manufacturers should be allowed only on the prescription of a *veterinarian*. Alternatively, such medicated feed may be prescribed by other suitably trained persons authorised to prescribe VMP containing *antimicrobial agent~~(s)~~* in accordance with the national legislation and under the supervision of a *veterinarian.* Animal feed manufacturers preparing medicated feed should do so following rules put in place by the *Competent Authority* in accordance with the national legislation. All medicated feed and medicated premixes should be appropriately labelled.

2) The regulations and recommendations on the responsible and prudent use of VMP containing *antimicrobial agent~~(s)~~* should be reinforced by animal feed manufacturers who should keep detailed records.

3) Use only approved sources of medications: Animal feed manufacturers preparing medicated feed should ensure that only approved sources of medications are added to feed at a level, purpose and species as permitted by the drug premix label or a veterinary prescription.

4) Ensure appropriate labelling with product identification, direction for use and withdrawal time: Animal feed manufacturers preparing medicated feed should ensure that medicated animal feed are labelled with the appropriate information (e.g. level of medication, approved claim, intended species, directions for use, warning, cautions) so as to ensure effective and safe use by the producer.

5) Implement appropriate production practices to prevent contamination of other feed: Animal feed manufacturers preparing medicated feed should implement appropriate production practices to avoid unnecessary carry over and unsafe cross contamination of unmedicated feed.

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